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**Boulton SJ, Bowman A, Koohgoli R, Birch-Machin MA. [Skin manifestations of mitochondrial dysfunction: more important than previously thought](#). *Experimental Dermatology* 2015, **24**(1), 12-13.**

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**DOI link to article:**

<http://dx.doi.org/10.1111/exd.12597>

**Date deposited:**

20/05/2015

**Embargo release date:**

01 January 2016



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Article Type: Commentary from the Editorial Board

## **Skin manifestations of mitochondrial dysfunction: more important than previously thought**

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**Short Title:** Skin manifestations of mitochondrial dysfunction

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### **Commentary**

Mitochondrial DNA (mtDNA) research is emerging within the dermatological field as a unique biomarker for diagnostic, prognostic and even therapeutic exploration. Since the first review of the role of mtDNA in skin disease was authored by our group some 14 years ago (1), there have been many exciting observations linking mitochondria to the defective structural, cell signaling, and oxidative damage pathways that promote skin disease manifestation. Feichtinger *et al* (2) have

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/exd.12597

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compiled an extensive and interesting review of recent literature that examines the relationship between known molecular paradigms of skin disease and intrinsic mitochondrial health. Whilst it is unrealistic for the authors to fully explore all recent advances within normal journal constraints, there are some surprising omissions, including our own detailed review of mtDNA and skin disease in 2000. Feichtinger *et al* (2) highlight the breadth of potential mitochondrial involvement in conditions not traditionally associated with metabolic or oxidative phosphorylation defects. On consideration however, it seems intuitive that any global defect of cell function is capable of exerting detrimental secondary effects on mitochondrial function. An example of this is mutation of the keratin 5 and 14 genes which are associated with the dermatological manifestation (e.g. skin blistering) of epidermolysis bullosa simplex. The altered mitochondrial network formation highlighted by Feichtinger *et al* (2), is likely to be a secondary factor in disease causation. Nonetheless, such mitochondrial aspects warrant investigation as potential therapeutic and prognostic markers within the context of wider disease state etiologies.

Mitochondria are the major site of ATP generation within cells. 5 enzyme complexes are involved in the generation of the energy currency molecule ATP. Complexes I-IV form the mitochondrial electron transport chain (mETC), whose primary function is the generation and maintenance of an electromotive proton gradient across the inner mitochondrial membrane as summarized in figure 1. Succinate dehydrogenase (Complex II) forms an important 'metabolic bridge' by performing a dual role as both a proximal mETC component and as an element of the tricarboxylic acid (TCA) cycle. It is known that several mtDNA mutations affecting genes encoding mETC components are complicit in defective mitochondrial function (recently reviewed in (3)).

Cells contain many copies of the mitochondrial genome, and as such may contain a ratio of mutant or damaged mtDNA to wildtype or undamaged mtDNA (termed 'heteroplasmy'). The threshold of tolerable accumulated damage can be breached over time, ultimately leading to the disease state manifestation (reviewed in (4)). Feichtinger *et al* (2) present several skin diseases involving mtDNA mutations; however discussion regarding the important effects of heteroplasmy with regard to disease development is missing possibly due to space constraints. Heteroplasmic effects are of critical importance, as mtDNA mutations may not be significant to cause a disease when present at only low levels within a cell (4)). The occurrence of heteroplasmy within the mitochondria allows damage to accumulate to a point without affecting mitochondrial function. This, along with limited repair mechanisms and lack of histone body association, permits the use of mtDNA as a reliable

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biomarker for damage accumulation in both human and animal skin (4,6,S1). Mutation in a nuclear or mitochondrial gene encoding an mETC subunit causes mitochondrial dysfunction, however impaired mtDNA maintenance, defects in mitochondrial translation factors, and other indirect mechanisms can also manifest disease states (reviewed in (S2)). In 2013, mitochondria-targeted transcription activator-like effector nucleases (mitoTALENs) were first demonstrated that cleave different classes of pathogenic mtDNA in dermal fibroblast cybrids (S3). Such mitoTALEN technology may present a novel therapeutic tool for targeting skin manifestations of mitochondrial disease.

Constant exposure to solar radiation, chemical and mechanical stresses places unique repair and protection pressures upon the skin compared to other organs. The damaging effects of UV irradiation upon mitochondrial damage and function in skin have been the subject of intensive recent investigation (S1, 4, S4). From our pioneering observation reported at the ESDR in 1996, the importance of using mtDNA as a reliable and sensitive biomarker of sun-exposure has been successfully exploited by our group and many others within dermatological areas including aging and cancer (reviewed in (S5, 6)). In addition, oxidative stress-induced mtDNA damage in skin cells has recently been used as a tool for assessing the potency of cell and mitochondria-targeted anti-oxidants (7) and has potential for screening therapeutic compounds including anti-oxidants used in cosmetics and the diet. This is alluded to by Feichtinger *et al* (2) who highlight nicotinamide (vitamin B3) a compound which, as a precursor of nicotinamide adenine dinucleotide within mitochondrial energy metabolism, has provided benefit by reducing actinic keratosis (S6) and mitochondrial myopathy (S7). Feichtinger *et al* (2) also briefly mention the therapeutic targeting of mitochondria in skin disease using the drug dithranol as a treatment for psoriasis. The mechanism of action was described as 'damaging' to mitochondria via the uncoupling of ATP production (2,S8). More recently, dithranol's mechanism of action has been elucidated (S9). The drug interacts specifically with the mitochondrial ubiquinone pool in keratinocyte cells subsequently inducing apoptosis by mitochondrial membrane potential disruption, causing a release in cytochrome c. This action is dependent upon the presence of a functional mETC (S9).

In the respect of a functional mETC, Feichtinger *et al* (2) have highlighted the important potential roles of individual mETC complexes in various skin diseases however Complex II was not explored. This often over-looked complex was recently implicated in the ageing process of both human (S10) and mouse skin (S11). It was also reported to produce reactive oxygen species (ROS) to a similar

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extent as Complexes I and III (8,S12,S13). The authors concluded that complex II may be more important than previously thought. Mutant Complex II subunits have been shown to increase ROS generation (S14-17), while Complex II ROS flux has also been shown to prevent cell cycle progress, inferring association with senescence induction (S18). Complex II's unique 'metabolic hinge' role in both the TCA cycle and the mETC dictates that the importance of this Complex is not to be underestimated. Further elucidation of Complex II's impact will provide a more complete picture of mitochondrial involvement in skin disease.

Without doubt, alterations in mitochondrial status and function impact skin health, although it is difficult to elucidate the individual contributions of UV irradiation, chemical insult, injury and genetic predisposition over a lifetime of stress and strain. Technological developments regarding real-time methods of ROS formation monitoring and miniaturized tools for mitochondrial analysis are pushing the boundaries of novel mitochondrial investigations and insight (S19,9). It is important that the momentum of skin-directed mitochondrial research is maintained; pioneering the research of biomarkers, etiologies and potential therapeutic strategies for the cure and prevention of such highly visible and life limiting diseases.

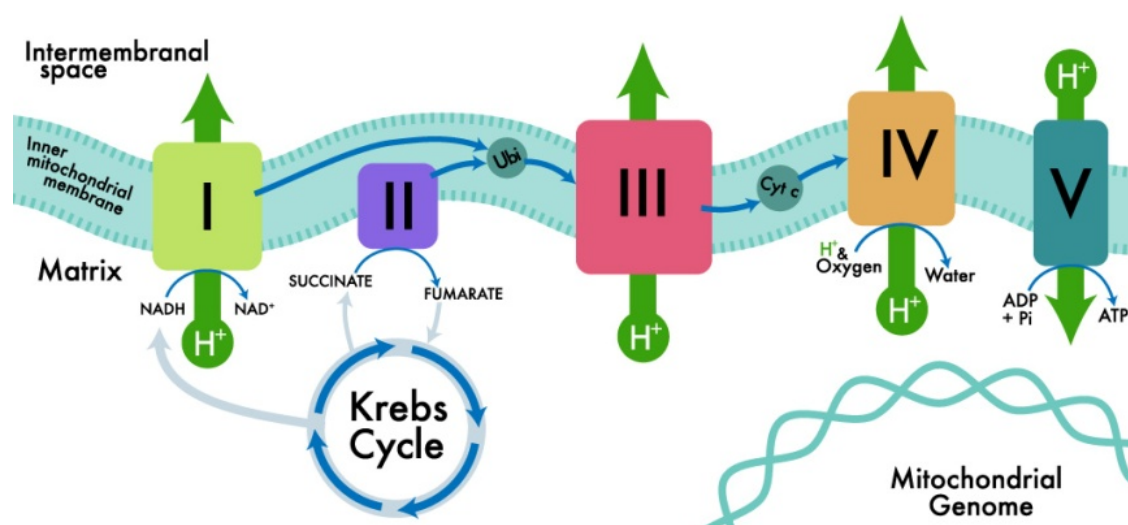
## Acknowledgements

The Research was supported by the National Institute for Health Research Newcastle Biomedical Research Centre based at Newcastle Hospitals Foundation Trust and Newcastle University. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. All authors contributed to writing the paper.

## Conflict of Interest

The authors report no conflicting interests

## Figures



**Figure 1:** Oxidative phosphorylation is performed by 5 enzyme Complexes located on the inner mitochondrial membrane. A proton motive gradient is maintained by Complexes I, III and IV pumping protons from the inner mitochondrial matrix into the intermembrane space. Electrons entry to the mETC from FADH is mediated by Complex II. The phosphorylation of ADP to ATP is performed by terminal enzyme Complex ATP synthase (Complex V) by coupling the reaction to the passive translocation of protons down the sustained gradient. With the exception of Complex II, the subunits comprising each Complex are encoded both by nuclear and mitochondrial genes; Complex II genes are encoded solely by the nuclear genome.

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